

**IN THE CLAIMS**

Please amend claims 30 and 31 as shown below. Please add new claims 45-64 as shown below. The following listing of claims replaces all prior listings.

1. (Canceled).
2. (Previously presented)      The article of manufacture of claim 30, wherein E<sub>1</sub>, E<sub>3</sub>, and E<sub>4</sub> are -O, and E<sub>2</sub> is -NH.
3. (Previously presented)      The article of manufacture of claim 30, wherein R<sub>1</sub> and R<sub>2</sub> are -H, alkyl, or substituted alkyl, and R<sub>3</sub> is hydroxy or alkoxy.
4. (Previously presented)      The article of manufacture of claim 30, wherein R<sub>1</sub> is substituted alkyl.
5. (Previously presented)      The article of manufacture of claim 4, wherein the substituted alkyl is a halogenated alkyl.
6. (Previously presented)      The article of manufacture of claim 5, wherein the halogenated alkyl is a chlorinated alkyl.
- 7-14. (Canceled)
15. (Withdrawn)      The method of claim 27, wherein the mammalian cell is human.
16. (Withdrawn)      The method of claim 27, wherein the disorder is characterized by the formation of neoplasms.
17. (Withdrawn)      The method of claim 16, wherein the neoplasms are selected from mammary, small-cell lung, non-small-cell lung, colorectal, leukemia, melanoma, pancreatic adenocarcinoma, central nervous system (CNS), ovarian, prostate, sarcoma of soft tissue or bone,

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head and neck, gastric which includes thyroid and non-Hodgkin's disease, stomach, myeloma, bladder, renal, neuroendocrine which includes thyroid and non-Hodgkin's disease and Hodgkin's disease neoplasms.

18. (Withdrawn)      The method of claim 17, wherein the neoplasms are colorectal neoplasms.

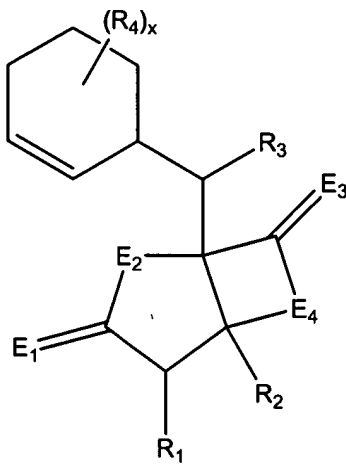
19. (Withdrawn)      A method for inhibiting proliferation of mammalian cells, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 23.

20. (Withdrawn)      The method of claim 19, wherein the mammalian cells are human.

21. (Withdrawn)      The method of claim 20, wherein the cells are selected from mammary, small-cell lung, non-small-cell lung, colorectal, leukemia, melanoma, pancreatic adenocarcinoma, central nervous system (CNS), ovarian, prostate, sarcoma of soft tissue or bone, head and neck, gastric, stomach, myeloma, bladder, renal, and neuroendocrine cells.

22-26. (Canceled)

27. (Withdrawn)      A method for treating a mammalian cell proliferative disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound having the structure:



# I

wherein:

R<sub>1</sub> to R<sub>3</sub> are each independently -H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, hydroxy, halogen, amino, amido, carboxyl,

-C(O)H, acyl, oxyacyl, carbamate, sulfonyl, sulfonamide, or sulfonyl,

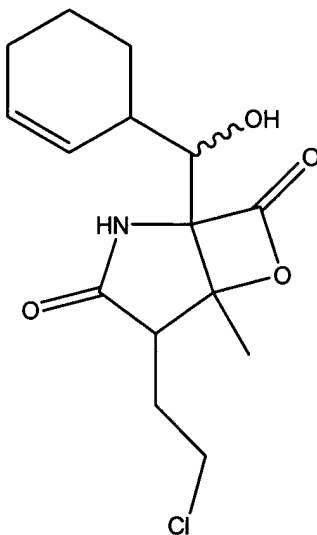
each R<sub>4</sub> is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl,

E<sub>1</sub> to E<sub>4</sub> are each independently -O, -NR<sub>5</sub>, or -S, wherein R<sub>5</sub> is -H or C<sub>1</sub>-C<sub>6</sub> alkyl, and

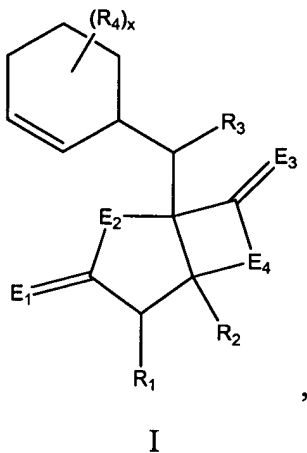
x is 0 to 8'

thereby treating a mammalian cell proliferative disorder.

28. (Withdrawn) The method of claim 27, wherein the compound has the structure:



29. (Withdrawn) A method for producing a compound having the ability to inhibit the proliferation of hyperproliferative mammalian cells, wherein said compound has structure (I):



wherein:

R<sub>1</sub> to R<sub>3</sub> are each independently -H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted

aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, hydroxy, halogen, amino, amido, carboxyl, -C(O)H, acyl, oxyacyl, carbamate, sulfonyl, sulfonamide, or sulfuryl,

each  $R_4$  is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl,

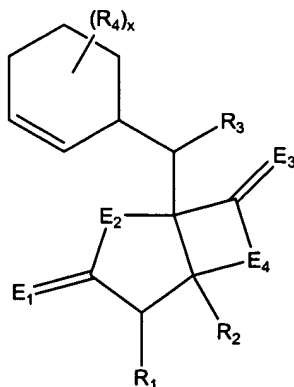
$E_1$  to  $E_4$  are each independently -O, -NR<sub>5</sub>, or -S, wherein R<sub>5</sub> is -H or C<sub>1</sub>-C<sub>6</sub> alkyl, and

x is 0 to 8,

the method comprising:

- a) cultivating a culture of a *Salinospora* sp. strain CNB392 or CNB476;
- b) isolating from the culture at least one compound of structure (I).

30. (Currently amended) An article of manufacture comprising packaging material and a pharmaceutical composition contained within said packaging material, wherein said packaging material comprises a label which indicates that said pharmaceutical composition can be used for treatment of a cell proliferative disorders and wherein said pharmaceutical composition comprises at least one compound having the structure (I):



(I)

wherein:

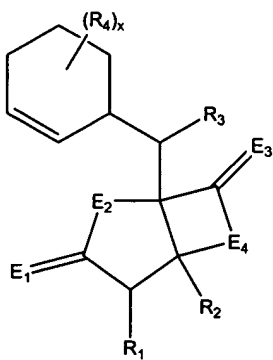
R<sub>1</sub> to R<sub>3</sub> are each independently -H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, hydroxy, halogen, amino, amido, carboxyl, -C(O)H, acyl, oxyacyl, carbamate, ~~sulfonyl~~, sulfonamide, ~~or~~ sulfuryl, or substituents comprising a sulfonyl moiety,

each R<sub>4</sub> is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl,

E<sub>1</sub> to E<sub>4</sub> are each independently -O, -NR<sub>5</sub>, or -S, wherein R<sub>5</sub> is -H or C<sub>1</sub>-C<sub>6</sub> alkyl, and

x is 0 to 8.

31. (Currently amended) A pharmaceutical composition ~~useful for inhibiting proliferation of hyperproliferative mammalian cells~~, comprising an effective amount of a compound having the structure (I) and a pharmaceutically acceptable carrier:



wherein:

R<sub>1</sub> to R<sub>3</sub> are each independently –H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, hydroxy, halogen, amino, amido, carboxyl, –C(O)H, acyl, oxyacyl, carbamate, ~~sulfonyl~~, sulfonamide, or sulfuryl, or substituents comprising a sulfonyl moiety,

each R<sub>4</sub> is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl,

E<sub>1</sub> to E<sub>4</sub> are each independently –O, –NR<sub>5</sub>, or –S, wherein R<sub>5</sub> is –H or C<sub>1</sub>–C<sub>6</sub> alkyl, and

x is 0 to 8,

and further comprising at least one additional anti-neoplastic agent other than the compound having the structure (I).

32. (Previously presented) The composition of claim 31, wherein E<sub>1</sub>, E<sub>3</sub>, and E<sub>4</sub> are –O, and E<sub>2</sub> is –NH.

33. (Previously presented) The composition of claim 31, wherein R<sub>1</sub> and R<sub>2</sub> are –H, alkyl, or substituted alkyl, and R<sub>3</sub> is hydroxy or alkoxy.

34. (Previously presented) The composition of claim 31, wherein R<sub>1</sub> is substituted alkyl.

35. (Previously presented) The composition of claim 34, wherein the substituted alkyl is a halogenated alkyl.

36. (Previously presented) The composition of claim 35, wherein the halogenated alkyl is a chlorinated alkyl.

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37. (Previously presented) The composition of claim 31, wherein the anti-neoplastic agent comprises an antimetabolite, an alkylating agent, a plant alkaloid, an antibiotic, a hormone, or an enzyme.

38. (Previously presented) The composition of claim 37, wherein the antimetabolite is selected from a group consisting of methotrexate, 5-fluorouracil, 6-mercaptopurine, cytosine arabinoside, hydroxyurea, and 2-chlorodeoxyadenosine.

39. (Previously presented) The composition of claim 37, wherein the alkylating agent is selected from a group consisting of cyclophosphamide, melphalan, busulfan, paraplatin, chlorambucil, and nitrogen mustard.

40. (Previously presented) The composition of claim 37, wherein the plant alkaloid is selected from a group consisting of vincristine, vinblastine, taxol, and etoposide.

41. (Previously presented) The composition of claim 37, wherein the antibiotic is selected from a group consisting of doxorubicin (adriamycin), daunorubicin, mitomycin c, and bleomycin.

42. (Previously presented) The composition of claim 37, wherein the hormone is selected from a group consisting of calusterone, diomostavolone, propionate, epitiostanol, mepitiothane, testolactone, tamoxifen, polyestradiol phosphate, megestrol acetate, flutamide, nilutamide, and trilotate.

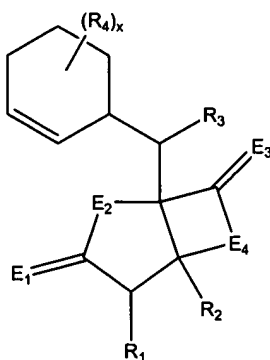
43. (Previously presented) The composition of claim 37, wherein the enzyme is selected from a group consisting of L-asparaginase derivatives and aminoacridine derivatives.

44. (Previously presented) The composition of claim 43, wherein the aminoacridine derivative is amsacrine.

45. (New) An article of manufacture comprising packaging material and a pharmaceutical composition contained within said packaging material, wherein said packaging material



comprises a label which indicates that said pharmaceutical composition can be used for treatment of a cell proliferative disorder and wherein said pharmaceutical composition comprises at least one compound having the structure (I):



(I)

wherein:

$R_1$  to  $R_3$  are each independently  $-H$ , alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, hydroxy, halogen, amino, amido, carboxyl,  $-C(O)H$ , acyl, oxyacyl, carbamate, sulfonamide, or sulfuryl, or substituents comprising a sulfonyl moiety,

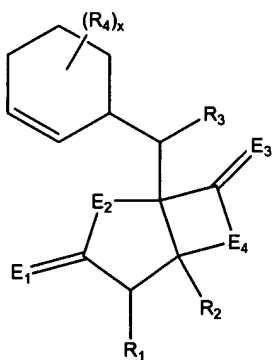
each  $R_4$  is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl,

$E_1$  to  $E_4$  are each independently  $-O$ ,  $-NR_5$ , or  $-S$ , wherein  $R_5$  is  $-H$  or  $C_1$ - $C_6$  alkyl, and

$x$  is 0 to 8,

wherein the cell proliferative disorder is colon cancer.

46. (New) The article of manufacture of claim 45, wherein  $E_1$ ,  $E_3$ , and  $E_4$  are  $-O$ , and  $E_2$  is  $-NH$ .
47. (New) The article of manufacture of claim 45, wherein  $R_1$  and  $R_2$  are  $-H$ , alkyl, or substituted alkyl, and  $R_3$  is hydroxy or alkoxy.
48. (New) The article of manufacture of claim 45, wherein  $R_1$  is substituted alkyl.
49. (New) The article of manufacture of claim 48, wherein the substituted alkyl is a halogenated alkyl.
50. (New) The article of manufacture of claim 49, wherein the halogenated alkyl is a chlorinated alkyl.
51. (New) A pharmaceutical composition, comprising an effective amount of a compound having the structure (I) and a pharmaceutically acceptable carrier:



wherein:

$R_1$  to  $R_3$  are each independently  $-H$ , alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic,

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substituted heterocyclic, cycloalkyl, substituted cycloalkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, hydroxy, halogen, amino, amido, carboxyl, -C(O)H, acyl, oxyacyl, carbamate, sulfonamide, or sulfuryl, or substituents comprising a sulfonyl moiety,

each R<sub>4</sub> is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl,

E<sub>1</sub> to E<sub>4</sub> are each independently -O, -NR<sub>5</sub>, or -S, wherein R<sub>5</sub> is -H or C<sub>1</sub>-C<sub>6</sub> alkyl, and

x is 0 to 8,

and further comprising at least one additional anti-neoplastic agent,

wherein the composition is useful for treatment of colon cancer.

52. (New) The composition of claim 51, wherein E<sub>1</sub>, E<sub>3</sub>, and E<sub>4</sub> are -O, and E<sub>2</sub> is -NH.

53. (New) The composition of claim 51, wherein R<sub>1</sub> and R<sub>2</sub> are -H, alkyl, or substituted alkyl, and R<sub>3</sub> is hydroxy or alkoxy.

54. (New) The composition of claim 51, wherein R<sub>1</sub> is substituted alkyl.

55. (New) The composition of claim 54, wherein the substituted alkyl is a halogenated alkyl.

56. (New) The composition of claim 55, wherein the halogenated alkyl is a chlorinated alkyl.

57. (New) The composition of claim 51, wherein the anti-neoplastic agent comprises an antimetabolite, an alkylating agent, a plant alkaloid, an antibiotic, a hormone, or an enzyme.

58. (New) The composition of claim 57, wherein the antimetabolite is selected from a group consisting of methotrexate, 5-fluorouracil, 6-mercaptopurine, cytosine arabinoside, hydroxyurea, and 2-chlorodeoxyadenosine.

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59. (New) The composition of claim 57, wherein the alkylating agent is selected from a group consisting of cyclophosphamide, melphalan, busulfan, parapl原因atin, chlorambucil, and nitrogen mustard.

60. (New) The composition of claim 57, wherein the plant alkaloid is selected from a group consisting of vincristine, vinblastine, taxol, and etoposide.

61. (New) The composition of claim 57, wherein the antibiotic is selected from a group consisting of doxorubicin (adriamycin), daunorubicin, mitomycin c, and bleomycin.

62. (New) The composition of claim 57, wherein the hormone is selected from a group consisting of calusterone, diomostavolone, propionate, epitioostanol, mepitioostane, testolactone, tamoxifen, polyestradiol phosphate, megestrol acetate, flutamide, nilutamide, and trilotane.

63. (New) The composition of claim 57, wherein the enzyme is selected from a group consisting of L-asparaginase derivatives and aminoacridine derivatives.

64. (New) The composition of claim 63, wherein the aminoacridine derivative is amsacrine.